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EMPIRICAL BAYES ESTIMATION OF CRITICAL DOSAGES HAVING SMALLEST --ETC(U)  
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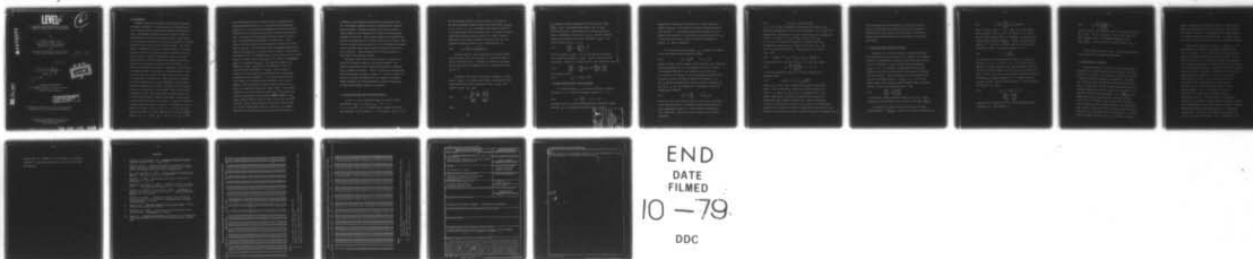
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6 EMPIRICAL BAYES ESTIMATION OF CRITICAL  
DOSAGES HAVING SMALLEST PREDICTIVE RISK.

by

10 Ora/Bialik and S./Zacks

Department of Research Medicine  
University of Pennsylvania

and

Department of Mathematics and Statistics  
Case Western Reserve University

14 TR-38

12 20p.

9 Technical Report, No. 38  
August 15, 1979

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SEP 27 1979  
REGULATED  
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11 15 Aug 79

PREPARED UNDER CONTRACT  
15 N 00014-75-C-0529 PROJECT NR 042-276  
OFFICE OF NAVAL RESEARCH

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## 1. Introduction

Consider a monotone relationship of the expected response to the dosage in bioassay. A critical dosage is considered here to be the treatment level associated with an expected response threshold. The problem of determining critical dosages is known as the calibration or the inverse regression problem. Many studies can be found in the literature concerning the estimation of critical dosages for linear and non-linear regression models. (Krutchkoff (1967)). Methods of estimation of critical dosages in the single sample case provide either point estimates or confidence intervals (Fieller (1964)). Among the methods which involve multistage design approach we find the stochastic approximation methods and sequential search procedures (Eichhorn and Zacks (1973)). The present study considers the problem of determining critical dosages in a situation where a large number of regression lines are available from many related assays, but each regression line is based on a small number of observations. Thus, rather than estimating the critical dosage for each assay individually, the inter-block information provided by the various regression lines is utilized to increase the precision of the estimates. This is done within a Bayesian framework. More specifically, the model assumes that in each assay the dosage - response relationship is represented by a linear regression, with the same variance  $\sigma^2$  around all regression lines and normal distribution of errors. The threshold,  $\eta$ , is the same for all assays. If  $\alpha_k$  and  $\beta_k$ ,  $k = 1, \dots, N$ , are the true intercept and slope of the  $k$ -th regression line, the  $k$ -th critical dosage is  $\xi_k = (\eta - \alpha_k) / \beta_k$ ,  $\beta_k > 0$  and  $\xi_k = \infty$  if  $\beta_k \leq 0$ . The



prior distribution of  $(\alpha, \beta)$  is chosen to yield a negligible prior marginal probability for  $\{\beta < 0\}$ . The Bayesian model assumes that  $(\alpha_k, \beta_k)$ ,  $k = 1, \dots, N$ , are priorly independent and identically distributed vectors with a properly chosen prior bivariate normal distribution. Let  $(a_k, b_k)$  be the least-square estimators (LSE) of  $(\alpha_k, \beta_k)$ , based on the observations performed in the  $k$ -th assay. On the basis of this LSE a posterior bivariate normal distribution is determined for  $(\alpha_k, \beta_k)$ . This distribution yields a predictive normal distribution, given  $(a_k, b_k)$  for a response  $Y(\xi)$  at a dosage  $\xi$ . (See Aitchison and Dunsmore 1975). The minimum predictive risk estimator of the critical dosage  $\xi_k$  is defined as the dosage,  $\hat{\xi}_k$ , which minimizes the predictive risk, i.e.,  $E\{(Y(\xi) - \eta)^2 | (a_k, b_k)\}$ . The suggested estimator of  $\xi_k$  depends on the LSE  $(a_k, b_k)$  and on the parameters of the prior bivariate normal distribution of  $(\alpha_k, \beta_k)$ . When the number of assays,  $N$ , is large an empirical Bayes method can be employed for estimating the prior parameters. In the present study we develop the formulae for the empirical Bayes estimation of the critical dosages. The formula obtained resembles somewhat Stein-type estimators of a multivariate mean vector (Zacks (1971)). The procedure developed in the present study is applied for the determination of critical concentrations of benzo-soluble organic extracts in air samples taken in 1963 and 1964 from 53 and 54 different sites in the U.S.A. These organic extracts were tested for their toxicity in a series of photodynamic bioassays (Epstien et. al. (1965)). The toxicity of the benzo-soluble extracts from the pollutants is

a function of their chemical composition and concentration in the air. The chemical composition varies (at random) within a site and between the sites. The model developed in the present study was found suitable for the determination of critical air concentrations (dosages) for each site. These critical dosages can be compared with the actual concentrations of the organic extracts in the samples. Whenever an air sample contains organic extracts with concentration higher than the critical dosage evidence exists of undesirable toxicity of the air pollution. Similar applications can also be performed in other areas of the empirical sciences.

The present study consists of five sections. In section 2 we specify the statistical model and the Bayesian framework. The method of determining critical dosages by minimizing the predictive risk is provided in section 3. Section 4 is devoted to the empirical Bayes approach when the number of assays,  $N$ , is large. Finally, in section 5 we present the application to the analysis of the photo-dynamic bioassays, for the determination of critical concentration of benzo-soluble organic extracts in air samples.

## 2. The Statistical Model and the Bayesian Framework.

Consider  $N$  sets of biological assays, having dose response relationship  $Y(x_{ki}) = \alpha_k + \beta_k x_{ki} + \epsilon_{ki}$ ,  $k = 1, \dots, N$ ,  $i = 1, \dots, n_k$ , where  $\epsilon_{ki}$  is a random variable normally distributed with expectation zero and variance  $\sigma^2$ . The regressors  $x_{ki} (i=1, \dots, n_k)$



are the log-dosage applied at the  $k$ th bioassay, and  $(\alpha_k, \beta_k)$  are the linear regression parameters based on the observations  $(y_{ki}, x_{ki})$ ,  $k = 1, \dots, N$ ,  $i = 1, \dots, n_k$ . The model assumes that the variance  $\sigma^2$  is the same around all the  $N$  regression lines. Determine the common least square estimators (LSE)  $a_k$  and  $b_k$  of the linear regression parameters and the variance around the regression line  $s_k^2$ . Let  $s_p^2$  denote the pooled estimator of this common variance, i.e.

$$(2.1) \quad s_p^2 = \frac{\sum_{k=1}^N (n_k - 2) s_k^2}{\sum_{k=1}^N (n_k - 2)}.$$

The large number of assays considered in the present problem and the typically small error variance,  $\sigma^2$ , provide estimates  $s^2$  with small standard error. Accordingly, we develop the following Bayesian model under the assumption that  $\sigma^2$  is known and substitute  $s_p^2$  for  $\sigma^2$ .

According to the theory of least-square estimation in normal models,  $(a_k, b_k)'$  is a random vector having a conditional bivariate normal distribution, with an expectation vector  $(\alpha_k, \beta_k)'$  and covariance matrix  $\Sigma_k$ , where

$$(2.2) \quad \Sigma_k = \sigma^2 \begin{pmatrix} \frac{1}{n} + \frac{\bar{x}_k}{SDX_k} & \frac{-\bar{x}_k}{SDX_k} \\ \frac{-\bar{x}_k}{SDX_k} & \frac{1}{SDX_k} \end{pmatrix},$$

where

$\bar{x}_k$  designates the mean log-dosage at the k'th assay and  $SDX_k = \sum_{i=1}^N (x_{ki} - \bar{x}_k)^2$ . The Bayesian model assumes that each assay can be considered as a random sample from a larger population of assays. Accordingly, we assume that  $(\alpha_k, \beta_k)$  follows a bivariate normal prior distribution with prior expectation  $(\alpha_0, \beta_0)'$  and prior covariance matrix,  $T$ ; i.e.,

$$(2.3) \quad \begin{pmatrix} \alpha_k \\ \beta_k \end{pmatrix} \sim N \left( \begin{pmatrix} \alpha_0 \\ \beta_0 \end{pmatrix}, T \right)$$

Given the estimates  $(a_k, b_k)'$  and  $t_k$ , the posterior distribution of the regression parameters  $(\alpha_k, \beta_k)'$  is also a bivariate normal distribution (Zacks 1971, Box and Tiao 1973) with expectation vector

$$(2.4) \quad \begin{pmatrix} \alpha_k^* \\ \beta_k^* \end{pmatrix} = \begin{pmatrix} \alpha_0 \\ \beta_0 \end{pmatrix} + T(I_k + T)^{-1} \left[ \begin{pmatrix} a_k \\ b_k \end{pmatrix} - \begin{pmatrix} \alpha_0 \\ \beta_0 \end{pmatrix} \right]$$

and covariance matrix

$$(2.5) \quad V_k = T - T'(I_k + T)^{-1}T.$$

### 3. Bayesian Determination of Critical Dosages.

The critical dosage,  $\xi_k$ , for the k-th bioassay, is defined as the value of  $x$  for which the expected response is  $\eta$ , i.e.,

$$(3.1) \quad \xi_k = \frac{\eta - \alpha_k}{\beta_k}, \quad k = 1, \dots, N.$$

We comment here that in practical applications of the model we assume that all  $\beta_k > 0$ . The Bayesian framework assumes a normal

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 
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marginal prior (posterior) distribution of  $\beta_k$ , which extends over negative values too. This problem is overcome in applications if the error variance  $\sigma^2$  is relatively small and the dosages in the bioassays are well designed. In such cases the posterior variance of  $\beta_k$  is often sufficiently small so that the posterior probability of negative  $\beta_k$  value is negligible.

In classical statistical analysis,  $\xi_k$  is frequently estimated by the least-squares inverse regression statistic

$$(3.2) \quad \tilde{\xi}_k = \frac{\eta - a_k}{b_k}, \quad k = 1, \dots, N.$$

Fieller's theorem (Fieller (1944)) is often applied to obtain classical confidence intervals for  $\xi_k$ . The application of Fieller's theorem in the Bayesian framework is not compatible with the definition (3.1) due to the interchange in the role of parameters and statistics.

We consider therefore two types of Bayes point estimators of  $\xi_k$ .

One is obtained by substituting in (3.1) the posterior estimates  $\alpha_k^*$  and  $\beta_k^*$  of  $\alpha_k$  and  $\beta_k$ , respectively. Accordingly, we obtain the (pseudo) Bayes estimator

$$(3.3) \quad \xi_k^* = \frac{\eta - \alpha_k^*}{\beta_k^*}, \quad k = 1, \dots, N.$$

Notice that  $\xi_k^*$  is not a Bayes estimator, since it does not minimize a prior (posterior) risk. We introduce a proper Bayes estimator of  $\xi_k$  by considering the value of  $x$  which minimizes the predictive risk  $E\{(Y(x) - \eta)^2\}$ . More specifically, we minimize the predictive expectation

$$(3.4) \quad Q(x; \mathcal{F}_k) = E\{(Y(x) - \eta)^2 | \mathcal{F}_k\},$$

$k = 1, \dots, N$ .  $E\{\cdot | \mathcal{F}_k\}$  designates the expectation with respect to the predictive distribution of  $Y(x)$  in the  $k$ -th bioassay. In the present case the predictive distribution is the normal distribution with mean  $\alpha_k^* + \beta_k^* x$  and variance  $\sigma^2 + V_k(x) = \sigma^2 + V_{k11} + 2xV_{k12} + x^2V_{k22}$ , where  $V_{kij}$ ,  $i, j = 1, 2$  are the elements of the posterior covariance matrix  $V_k$ . We apply here the loss function  $(Y(\hat{\xi}_k) - \eta)^2$  rather than  $(\tilde{\xi}_k - \xi_k)^2$  since the posterior expectation of  $(\eta - \alpha_k)/\beta_k$ , given  $\mathcal{F}_k$ , does not exist. Thus

$$(3.5) \quad Q(x; \mathcal{F}_k) = \sigma^2 + V_{k11} + 2xV_{k12} + x^2V_{k22} + (\alpha_k^* + \beta_k^* x - \eta)^2.$$

The minimization of (3.4) with respect to  $x$  yields the estimator

$$(3.6) \quad \hat{\xi}_k = \frac{\xi_k^* - V_{k12}/\beta_k^*}{1 + V_{k22}/\beta_k^*}, \quad k = 1, \dots, N.$$

A  $(1-\alpha)$  level predictive interval for  $Y(\hat{\xi})$  is specified by the prediction limits

$$(3.7) \quad P(\hat{\xi}; \alpha) = \alpha^* + \beta^* \hat{\xi} \pm z_{1-\alpha/2} \sqrt{Q(\hat{\xi})}.$$

where  $z_{1-\alpha/2}$  is the  $1-\alpha/2$  fractile of the standard normal distribution. It is not difficult to show that the three different estimators of  $\xi_k$ , namely  $\tilde{\xi}_k$ ,  $\xi_k^*$  and  $\hat{\xi}_k$  are consistent ones, as the number of observations  $n_k$  around the regression lines increase to infinity and  $SDX_k$  increase to infinity too. However, questions of consistency and asymptotic efficiency are irrelevant to our problem since generally we are concerned with cases of small number of observations in each bioassay. For this reason we adopted the Bayesian approach to compensate for the



lack of accuracy due to this deficiency. As we show in the next section, an empirical Bayes approach can utilize the information obtained from the large number of different assay to determine an adequate common prior distribution for the analysis of the individual assays.

#### 4. An Empirical Bayes Approach for Large N.

Generally it is a difficult problem to determine that proper prior parameters for each regression line. However, if the analysis consists of a large number of regression lines from different assays, and if it is plausible to assume that the regression parameters  $(\alpha_k, \beta_k)$ ,  $k = 1, \dots, N$ , constitute a random sample from the sample bivariate (prior) normal distribution, one can estimate consistently the prior parameters. More specifically, under the assumption that the (true) regression parameters  $(\alpha_k, \beta_k)$ ,  $k = 1, \dots, N$ , are independent random vectors having the same bivariate normal distribution, with mean  $(\alpha_0, \beta_0)$  and covariance matrix  $T$  then

$$(4.1) \quad \begin{pmatrix} \hat{\alpha}_0 \\ \hat{\beta}_0 \end{pmatrix} = \frac{1}{N} \sum_{k=1}^N \begin{pmatrix} a_k \\ b_k \end{pmatrix}$$

is an unbiased, strongly consistent estimator of  $(\alpha_0, \beta_0)'$  having a bivariate normal distribution with covariance matrix  $\frac{1}{N}(T + \frac{1}{N} \sum_{k=1}^N t_k)$ .

An unbiased and strongly consistent estimator of the total covariance matrix  $T + \frac{1}{N} \sum_{k=1}^N t_k$  is given by the sample covariance matrix

$$(4.2) \quad C = \frac{1}{N-1} \begin{pmatrix} a' \\ b' \end{pmatrix} (I_N - \frac{1}{N} J_N) (a, b)$$

where  $a' = (a_1, \dots, a_N)$ ,  $b' = (b_1, \dots, b_N)$ ,  $I_N$  is the identity matrix of order  $N$  and  $J_N$  is an  $N \times N$  matrix of 1's. Notice that the total covariance matrix  $T + \frac{1}{N} \sum_{k=1}^N t_k$  is composed of the "within variance" component  $\frac{1}{N} \sum_{k=1}^N t_k$  and the "between variance" component  $T$ . Thus as in the common components of variance model (see Graybill (1976)) and unbiased estimator of  $T$  is

$$(4.3) \quad \hat{T} = C - \frac{1}{N} \sum_{k=1}^N t_k$$

We remark that if the design matrices of all the  $N$  assays are the same, i.e.,  $t_k = t$  for all  $k = 1, \dots, N$ , the above formulae simplify. We further remark that (4.3) may be negative definite, if the "within variance" component is large and  $N$  is not sufficiently large. If this is the case, one has to apply a different approach, or use biased but consistent estimators of  $T$ . Finally, given the estimates  $(\hat{\alpha}_0, \hat{\beta}_0)$  and the unbiased estimator  $\hat{T}$  one can determine an estimate of  $v_k$ , namely

$$(4.4) \quad \hat{v}_k = \hat{T} - \hat{T} (t_k + \hat{T})^{-1} \hat{T} \\ = \begin{pmatrix} \hat{v}_{k11} & \hat{v}_{k12} \\ \hat{v}_{k12} & \hat{v}_{k22} \end{pmatrix}$$

and substitute its elements in (3.6) to obtain an empirical Bayes estimate of  $\xi_k$ . This estimator is



$$(4.5) \quad \hat{\xi}_k = \frac{\hat{\xi}_k^* - \hat{v}_{k12}/\hat{\beta}_k^2}{1 + \hat{v}_{k22}/\hat{\beta}_k^2},$$

where  $\hat{\alpha}_k$  and  $\hat{\beta}_k$  are obtained from (2.4) by substituting  $(\hat{\alpha}_0, \hat{\beta}_0)'$  for  $(\alpha_0, \beta_0)'$  and  $\hat{\xi}_k^* = (n - \hat{\alpha}_k)/\hat{\beta}_k$ . Notice that the empirical

Bayes estimator (4.5) is a shrinkage estimator whenever

$-\hat{v}_{k12} \leq \hat{\xi}_k^* \hat{v}_{k22}$  This is the case, in particular when  $\hat{v}_{k12} > 0$ .

In the following section we provide a large scale application of the empirical Bayes approach described above.

## 5. An Application of the Model.

The model discussed in the previous sections was applied to the analysis of a large scale photodynamic bioassays, performed by Epstein et. al. (1965), for the purpose of evaluating the toxicity of organic extracts from atmospheric pollutants. Air samples were collected in 1963 and 1964 from 53 and 54 different sites in the U.S., respectively. The benzo-soluble organic particles were chemically extracted from the air samples and the atmospheric concentrations [g/m<sup>3</sup> of air] were recorded. Proper solutions of the organic extracts (O.E.) were tested at three dilution levels  $d = 10^{-4}, 10^{-5}, 10^{-6}$  [g/ml]. These preparations were applied in wells including 30 cells of *Paramecia Caudatum*. The measured response, called the LT90, was the time (in minutes) required to immobilise 90% of the cells under ultra-violet irradiation. The measurement of response was truncated at  $t_0 = 90$  minutes. Response

values over 90 minutes are therefore unavailable, neither the proportion of living cells at the time of truncation. Four replicas were performed at each dose. Simultaneously, the LT90 was measured on a standard synthetic benzo-a-pyrene (BaP). 41 complete assays of the 1963 data and 54 of the 1964 data were available for analysis.

For the statistical analysis define  $x = -\log_{10} d - 5$ . The model assumes that  $\ln(\text{LT90})$  is normally distributed with mean  $\alpha + \beta x$  and variance  $\sigma^2$ . This model links the analysis described later to the theory developed in the previous sections. Bialik (1978) verified that the  $\ln \text{LT90}$  versus log-dose regression lines of the standard preparations, correspond to each year of test data, were not significantly different. Accordingly, the analysis presented here does not have to adjust the regression line of each site for varying experimental conditions. In Table 1 we present the basic response statistics, the regression statistic and the expected LT90 corresponding to the actual concentration in the air for sites of the 1963 samples. The regression parameters  $(\alpha, \beta)$  of different sites are not expected to be the same due to the different chemical composition of the O.E.. Since the toxicity of the organic pollutants is a combination of their chemical composition and atmospheric concentration, Bialik (1978) introduced a measure of toxicity, AIRLT90, which takes into account both factors. An equivalent air-dosage, AD, is defined as the atmospheric concentration of the O.E. in a given site solved in 1 ml of preparation. Let

$$(5.1) \quad \text{XAIR} = -\log_{10}(\text{AD}) - 5.$$

Then the corresponding predicted LT90 is given by

$$(5.2) \quad \text{AIRLT90} = \exp(a + b \cdot \text{XAIR} + \hat{\sigma}^2/2).$$

The XAIR and AIRLT90 of the various sites are given in Table 1.

Notice that all the XAIR values in Table 1 fall in the experimental domain  $(-1 \leq x \leq 1)$ . Accordingly, the AIRLT90 values are not based on extrapolation. We also remark that intensive photodynamic activity is associated with low LT90 values.

In Table 2 we present the Bayes estimator  $(\alpha_k^*, \beta_k^*)$  and the corresponding  $\tilde{\xi}_k$ ,  $\xi_k^*$  and  $\hat{\xi}_k$  estimators of the inverse regression parameters corresponding to the threshold  $\eta = 2.9$ . This value of  $\eta$  is the smallest  $\ln(\text{AIRLT90})$  in Table 1. The Bayes estimators  $(\alpha_k^*, \beta_k^*)$  were determined according to the empirical Bayes approach, described in Section 4, based on the 1963 and 1964 data. The LSE's  $(a_k, b_k)$  of the 1963 data yield the empirical Bayes estimates

$$(5.3) \quad \begin{pmatrix} \hat{\alpha}_0 \\ \hat{\beta}_0 \end{pmatrix}_{63} = \begin{pmatrix} 3.8628 \\ 0.9241 \end{pmatrix}$$

The corresponding covariance matrix is

$$(5.4) \quad (C)_{63} = \begin{pmatrix} .1645 & .0354 \\ .0354 & .0723 \end{pmatrix}$$



The corresponding covariance matrix for the 1963 data is

$$(5.5) \quad (\bar{\xi}_k)_{63} = \begin{pmatrix} .0018 & .0017 \\ .0017 & .0035 \end{pmatrix} .$$

Thus, the empirical Bayes estimate of the prior covariance matrix T is

$$(5.6) \quad (T)_{63} = \begin{pmatrix} .1627 & .0337 \\ .0337 & .0683 \end{pmatrix} .$$

We computed similar estimates based on the 1964 data and obtained

$$(5.7) \quad \begin{pmatrix} \hat{\alpha}_0 \\ \hat{\beta}_0 \end{pmatrix}_{64} = \begin{pmatrix} 3.5551 \\ 1.0673 \end{pmatrix} , \quad (T)_{64} = \begin{pmatrix} .2437 & .0232 \\ .0232 & .0718 \end{pmatrix}$$

For the purpose of comparison we present in Table 2 for each site of the 1963 samples the empirical Bayes estimates corresponding to 1963 and 1964.

Observe that the values of  $(\alpha_k^*, \beta_k^*)'$  are very close to  $(a_k, b_k)' \pm (S.D.(a_k), S.D.(b_k))'$ . As a result  $\hat{\xi}_k$  and  $\xi_k^*$  have similar values. Also  $.0001 \leq |\hat{\xi}_k - \xi_k^*| \leq .0623$  for every  $k = 1, \dots, 41$ . However, a visible effect on  $\hat{\xi}_k$  and  $\xi_k^*$  is demonstrated by changing the prior distribution, corresponding to changes in the experimental conditions. This can be seen when the empirical prior distribution based on the 1964 data is applied to the 1963 data. Finally, the predicted response at XAIR,  $Y^*(XAIR) = \alpha^* + \beta^* XAIR$ , can be compared with the  $\gamma$ -fractile of the predictive distribution at  $\hat{\xi}$ , namely

$$(5.8) \quad TL_Y = \alpha^* + \beta^* \hat{\xi} + z_Y \sqrt{Q(\hat{\xi})} .$$



In other words, if  $Y^*(XAIR) > TL_Y$  we conclude, with predictive confidence  $\gamma$ , that the toxicity of the O.E. in the air is below the threshold.

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Table 1: Response Statistics of the Organic Extracts and the AIRLT90 for the 1963 Data

SITE N	NEAN LT90	EXPECTED LT90	ST. DEV. LT90	A	B	$\hat{\sigma}$	SE{A}	SE{B}	R	AIRLT90							
2	12	22.83	63.11	85.96	25.69	49.86	96.76	0.7	5.5	10.1	3.908	0.663	0.37	0.56	0.68	0.954	54.37
3	8	28.50	59.59	85.59	28.50	59.62	124.74	1.1	4.6	6.3	4.087	0.738	0.36	0.95	0.135	0.996	55.62
4	12	13.55	26.93	85.59	12.50	31.53	79.54	1.6	6.3	63.6	3.447	0.925	0.93	0.88	0.108	0.984	31.48
5	8	11.47	22.79	85.59	11.46	22.82	45.44	0.4	1.5	1.5	3.126	0.689	0.54	1.16	0.165	0.991	21.77
6	8	26.15	85.96	85.59	26.13	86.08	283.31	2.0	21.6	21.6	4.454	1.192	0.54	1.16	0.165	0.997	91.90
7	8	14.55	38.98	85.59	14.55	39.01	104.56	0.5	3.5	3.5	3.653	0.986	0.48	1.09	0.155	0.996	46.31
8	8	11.05	39.37	85.59	11.04	39.40	140.59	0.2	2.7	2.7	3.673	1.272	0.42	1.03	0.146	0.998	28.66
9	12	15.41	38.35	83.70	15.75	36.71	85.57	0.1	0.6	2.8	3.603	0.846	0.20	0.41	0.050	0.999	32.14
10	8	13.90	61.18	85.59	13.90	61.22	269.64	0.3	5.7	5.7	4.114	1.483	0.39	0.99	0.139	0.999	61.03
11	12	14.68	40.49	89.69	15.21	37.65	93.15	0.5	3.5	17.0	3.627	0.906	0.46	0.62	0.076	0.996	32.76
12	8	31.62	89.82	89.82	31.61	53.30	89.88	1.3	13.0	10.5	3.975	0.523	0.36	0.67	0.067	0.998	55.98
13	12	9.53	26.48	76.80	9.46	26.87	76.32	0.3	2.1	17.9	3.290	1.044	0.55	0.68	0.083	0.998	25.33
14	8	30.61	64.62	85.59	30.61	64.64	136.48	0.5	2.4	2.4	4.168	0.747	0.24	0.78	0.110	0.998	65.00
16	8	19.43	52.30	85.59	19.44	52.31	140.74	0.9	6.3	6.3	3.956	0.990	0.48	1.10	0.155	0.996	59.06
17	8	28.25	72.73	85.59	28.23	72.89	188.20	4.4	29.0	29.0	4.286	0.949	0.74	1.36	0.193	0.991	78.16
18	8	15.45	43.63	85.59	15.70	45.67	132.85	15.9	138.8	138.8	3.789	1.068	0.254	0.252	0.356	0.925	50.51
19	8	16.91	30.31	85.59	16.90	30.43	54.79	2.9	9.4	9.4	3.410	0.588	0.101	0.159	0.225	0.958	27.21
20	10	14.95	35.61	89.21	14.82	36.21	88.46	2.2	12.5	78.4	3.584	0.893	0.99	1.03	0.133	0.992	34.26
22	8	36.57	79.85	85.59	36.49	80.22	176.36	12.9	61.5	61.5	4.380	0.788	0.98	1.56	0.221	0.978	81.84
23	8	23.58	51.94	85.59	23.59	51.94	114.40	0.6	2.8	2.8	3.950	0.790	0.32	0.89	0.126	0.998	57.38
30	8	11.11	21.11	85.59	11.13	21.11	40.04	0.7	2.7	2.7	3.047	0.640	0.77	0.139	0.197	0.979	18.95
31	10	10.96	20.53	89.99	9.71	26.18	70.59	0.1	0.5	8.8	3.265	0.992	0.33	0.59	0.077	0.964	25.19
32	8	12.23	43.77	85.59	12.23	43.81	156.85	0.5	5.8	5.8	3.778	1.276	0.55	1.17	0.166	0.997	44.24
33	8	18.26	46.46	85.59	18.26	46.73	119.60	1.5	9.8	9.8	3.842	0.940	0.67	1.30	0.183	0.992	46.72
34	8	11.09	40.51	85.59	11.09	40.53	148.13	0.1	1.8	1.8	3.701	1.296	0.33	0.91	0.129	0.999	32.36
37	8	24.18	44.79	85.59	24.19	44.80	82.96	1.1	3.7	3.7	3.801	0.616	0.43	1.04	0.147	0.993	44.98
43	8	21.96	69.43	85.59	21.97	69.45	219.52	1.3	12.6	12.6	4.239	1.151	0.51	1.13	0.160	0.997	69.77
44	8	20.34	48.53	85.59	20.35	48.53	115.77	0.2	0.9	0.9	3.682	0.869	0.20	0.71	0.101	0.999	52.21
45	12	14.29	36.76	74.32	14.87	33.92	77.38	0.1	0.8	3.2	3.524	0.825	0.24	0.45	0.055	0.996	31.29
47	8	23.32	46.34	85.59	23.34	46.33	91.99	1.4	5.4	5.4	3.835	0.686	0.50	1.11	0.157	0.992	41.73
48	8	28.81	73.76	85.59	28.75	74.10	190.98	8.3	54.7	54.7	4.300	0.947	1.00	1.50	0.224	0.984	71.75
49	8	44.14	84.83	85.59	44.13	84.87	163.20	2.3	8.3	8.3	4.441	0.654	0.34	0.92	0.131	0.996	186.99
50	8	28.70	72.96	85.59	28.69	72.96	185.55	0.8	5.4	5.4	4.289	0.933	0.32	0.89	0.126	0.998	183.98
51	8	23.57	84.22	85.59	23.58	84.24	300.93	1.1	13.7	13.7	4.433	1.273	0.44	1.04	0.148	0.908	97.37
52	8	18.41	40.69	85.59	18.40	40.71	90.06	0.4	2.0	2.0	3.706	0.794	0.35	0.09	0.133	0.907	43.64
53	8	24.55	86.73	85.59	24.54	86.85	307.35	1.7	21.2	21.2	4.463	1.264	0.53	1.15	0.162	0.997	64.60
54	9	21.87	34.31	93.61	20.59	38.85	73.30	3.1	7.6	56.3	3.656	0.635	0.80	1.06	0.142	0.949	39.95
55	8	10.45	57.48	85.59	10.49	57.82	318.86	4.0	120.2	120.2	4.039	1.707	1.89	0.217	0.308	0.982	33.56
56	12	10.93	28.75	71.18	11.02	28.30	72.67	3.9	27.2	166.8	3.327	0.943	1.80	1.22	0.150	0.980	32.08
57	8	24.42	69.84	85.59	24.39	70.03	201.19	3.8	31.3	31.3	4.246	1.055	0.80	1.42	0.200	0.991	90.38
59	8	35.35	85.64	85.59	35.35	85.64	207.47	0.9	5.3	5.3	4.450	0.885	0.27	0.81	0.115	0.999	91.44

## Notes:

- 1) N is the number of observations around each line.
- 2) Expected LT90 =  $\exp\{A + BX + \hat{\sigma}^2/2\}$ .
- 3) A and B are the least squares estimates,  $\hat{\sigma}$  is the standard deviation around the regression lines.
- 4) AIRLT90 =  $\exp\{A + BXAIR + \hat{\sigma}^2/2\}$ , XAIR is given Table 2

Table 2: The Actual and the Critical Atmospheric Concentrations of Organic Extracts for 1963 Data

SITE	N	A	B	A <sub>63</sub>	B <sub>63</sub>	A <sub>64</sub>	B <sub>64</sub>	XAIR	$\tilde{\xi}_{63}$	$\xi_{63}^*$	$\hat{\xi}_{63}$	$\tilde{\xi}_{64}$	$\xi_{64}^*$	$\hat{\xi}_{64}$
2	12	3.908	0.663	3.908	0.664	3.908	0.664	0.1318	-1.5204	-1.5184	-1.5178	-1.5204	-1.5176	-1.5170
3	8	4.087	0.738	4.088	0.740	4.088	0.741	-0.0929	-1.6084	-1.6084	-1.6040	-1.6084	-1.6039	-1.6026
4	12	3.447	0.925	3.447	0.923	3.447	0.927	0.0031	-0.5914	-0.5945	-0.5938	-0.5914	-0.5903	-0.5895
5	8	3.126	0.899	3.130	0.894	3.130	0.897	-0.0663	-0.3280	-0.3315	-0.3320	-0.3280	-0.3306	-0.3311
6	8	4.454	1.192	4.450	1.186	4.451	1.189	0.0564	-1.3037	-1.3065	-1.3057	-1.3037	-1.3049	-1.3041
7	8	3.663	0.986	3.663	0.985	3.663	0.987	0.1754	-0.7738	-0.7746	-0.7743	-0.7738	-0.7733	-0.7730
8	8	3.673	1.272	3.671	1.268	3.672	1.269	-0.2492	-0.6077	-0.6077	-0.6085	-0.6077	-0.6079	-0.6078
9	12	3.603	0.846	3.603	0.846	3.603	0.846	-0.1564	-0.8310	-0.8310	-0.8310	-0.8310	-0.8308	-0.8307
10	8	4.114	1.483	4.111	1.477	4.111	1.478	-0.0002	-0.8186	-0.8200	-0.8198	-0.8186	-0.8194	-0.8193
11	12	3.627	0.906	3.627	0.906	3.627	0.907	-0.1521	-0.8024	-0.8028	-0.8026	-0.8024	-0.8018	-0.8015
12	8	3.975	0.523	3.977	0.527	3.977	0.528	0.0954	-2.0554	-2.0437	-2.0401	-2.0554	-2.0412	-2.0376
13	12	3.290	1.044	3.291	1.043	3.290	1.044	-0.0552	-0.3736	-0.3751	-0.3750	-0.3736	-0.3738	-0.3737
14	8	4.168	0.747	4.168	0.748	4.168	0.748	0.0081	-1.6975	-1.6960	-1.6954	-1.6975	-1.6954	-1.6948
16	8	3.956	0.990	3.955	0.989	3.956	0.991	0.1241	-1.0667	-1.0672	-1.0665	-1.0667	-1.0657	-1.0650
17	8	4.286	0.949	4.284	0.948	4.285	0.952	0.0767	-1.4605	-1.4595	-1.4567	-1.4605	-1.4553	-1.4525
18	8	3.789	1.068	3.774	1.022	3.779	1.064	0.1248	-0.8324	-0.8548	-0.8475	-0.8324	-0.8264	-0.8200
19	8	3.410	0.588	3.424	0.611	3.426	0.620	-0.1812	-0.8673	-0.8573	-0.8529	-0.8673	-0.8484	-0.8441
20	10	3.584	0.893	3.586	0.893	3.584	0.897	-0.0562	-0.7660	-0.7680	-0.7668	-0.7660	-0.7629	-0.7617
22	8	4.380	0.788	4.380	0.797	4.383	0.802	0.0317	-1.8782	-1.8569	-1.8474	-1.8782	-1.8476	-1.8382
23	8	3.950	0.790	3.950	0.791	3.951	0.792	0.1268	-1.3291	-1.3279	-1.3272	-1.3291	-1.3269	-1.3262
30	8	3.047	0.640	3.056	0.652	3.057	0.658	-0.1639	-0.2297	-0.2399	-0.2416	-0.2297	-0.2387	-0.2404
31	10	3.265	0.992	3.265	0.992	3.265	0.992	-0.0380	-0.3679	-0.3685	-0.3685	-0.3679	-0.3680	-0.3680
32	8	3.778	1.276	3.775	1.268	3.776	1.272	0.0091	-0.6891	-0.6897	-0.6896	-0.6891	-0.6886	-0.6884
33	8	3.842	0.940	3.842	0.939	3.843	0.943	0.0023	-1.0021	-1.0025	-1.0013	-1.0021	-0.9995	-0.9983
34	8	3.701	1.296	3.700	1.293	3.700	1.294	-0.1731	-0.6181	-0.6186	-0.6185	-0.6181	-0.6182	-0.6181
37	8	3.801	0.616	3.803	0.620	3.803	0.621	0.0082	-1.4627	-1.4561	-1.4538	-1.4627	-1.4536	-1.4513
43	8	4.239	1.151	4.236	1.147	4.237	1.149	0.0053	-1.1633	-1.1653	-1.1646	-1.1633	-1.1638	-1.1631
44	8	3.882	0.869	3.882	0.869	3.882	0.869	0.0844	-1.1300	-1.1299	-1.1297	-1.1300	-1.1296	-1.1294
45	12	3.524	0.825	3.524	0.825	3.524	0.825	-0.0975	-0.7564	-0.7564	-0.7564	-0.7564	-0.7561	-0.7560
47	8	3.835	0.686	3.837	0.690	3.838	0.692	-0.1504	-1.3630	-1.3574	-1.3551	-1.3630	-1.3545	-1.3523
48	8	4.300	0.947	4.296	0.945	4.298	0.952	-0.0284	-1.4784	-1.4762	-1.4712	-1.4784	-1.4688	-1.4638
49	8	4.441	0.634	4.441	0.636	4.442	0.637	1.2091	-2.3563	-2.3488	-2.3464	-2.3563	-2.3472	-2.3448
50	8	4.289	0.933	4.289	0.934	4.289	0.934	0.9917	-1.4887	-1.4884	-1.4879	-1.4887	-1.4876	-1.4870
51	8	4.433	1.273	4.430	1.268	4.431	1.270	0.1305	-1.2042	-1.2064	-1.2060	-1.2042	-1.2054	-1.2050
52	8	3.706	0.794	3.707	0.795	3.707	0.796	0.0712	-1.0151	-1.0145	-1.0140	-1.0151	-1.0135	-1.0130
53	8	4.463	1.264	4.459	1.257	4.459	1.259	-0.2328	-1.2366	-1.2398	-1.2391	-1.2366	-1.2383	-1.2376
54	9	3.656	0.635	3.658	0.642	3.658	0.644	0.0493	-1.1906	-1.1823	-1.1791	-1.1906	-1.1769	-1.1737
55	8	4.039	1.707	3.964	1.545	3.969	1.577	-0.3079	-0.6673	-0.6839	-0.6877	-0.6673	-0.6781	-0.6770
56	12	3.327	0.943	3.337	0.935	3.329	0.949	-0.1501	-0.4528	-0.4672	-0.4652	-0.4528	-0.4524	-0.4509
57	8	4.246	1.055	4.241	1.049	4.243	1.054	0.2448	-1.2758	-1.2785	-1.2764	-1.2758	-1.2744	-1.2723
59	8	4.450	0.885	4.450	0.885	4.450	0.886	0.0746	-1.7514	-1.7507	-1.7501	-1.7514	-1.7501	-1.7495

## Notes:

- 1)  $A_{63}$ ,  $A_{64}$ ,  $B_{63}$  and  $B_{64}$  are the Bayes estimates of  $(\alpha, \beta)$  based on the empirical Bayes of 1963 and 1964.
- 2) XAIR is the dosage equivalent of the actual air concentration of O.E.
- 3)  $\tilde{\xi}$ ,  $\xi^*$ ,  $\hat{\xi}$  are the critical atmospheric concentrations (dosages) relative to  $\eta = 2.9$



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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER Technical Report No. 38	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) EMPIRICAL BAYES ESTIMATION OF CRITICAL DOSAGES HAVING SMALLEST PREDICTIVE RISK.		5. TYPE OF REPORT & PERIOD COVERED Technical Report
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Ora Bialik and S. Zacks		8. CONTRACT OR GRANT NUMBER(s) N 00014-75-C-0529 PROJECT NR 042-276
9. PERFORMING ORGANIZATION NAME AND ADDRESS Department of Mathematics & Statistics Case Western Reserve University Cleveland, Ohio		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS OFFICE OF NAVAL RESEARCH ARLINGTON, VIRGINIA 22217		12. REPORT DATE August 15, 1979
		13. NUMBER OF PAGES 15
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) UNCLASSIFIED
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report)  APPROVED FOR PUBLIC RELEASE: DISTRIBUTION UNLIMITED.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Linear regression, Bayes estimates, empirical Bayes, critical dosages, calibration, predictive risk, photodynamic bioassays. $x_i(\eta)$ $x_i$ $\alpha$ $\beta$		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) An empirical Bayes procedure is developed for the estimation of critical dosages in the linear regression case. If $Y = \alpha + \beta x + e$ is the basic linear model, the critical dosage is defined as $\xi(\eta) = (\eta - \alpha)/\beta$ , for $\beta > 0$ . A new type of Bayes estimator of $\xi(\eta)$ is derived under the criterion of minimizing the predictive risk $E[(\alpha + \beta \xi - \eta)^2   \mathcal{F}_n]$ . The empirical Bayes procedure provides consistent estimators of the prior parameters when a large number of independent repetitions of the experiment is available. The methodology is developed to,		

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analyze a large set of photodynamic bioassays, for the determination of critical air concentrations of benzo-soluble organic extracts.